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〔Original Paper〕

Metabolic imaging with positron emission tomography for the evaluation of left ventricular wall motion reversibility in patients with idiopathic dilated cardiomyopathy

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SUMMARY

Twenty idiopathic dilated cardiomyopathy (IDC) patients who demonstrated reduction of left ventricular (LV) ejection fraction (LVEF) evaluated by echocardiography (mean±s.d.: 34.1±10.4%) underwent positron emission tomography with 18Fluorine-Fluorodeoxyglucose (FDG-PET) study after oral glucose loading. Regional myocardial glucose utilization rate (rMGU) and coefficient of variance (CV) of rMGU were measured and calculated for each patient. The patients were divided into two group by the median of the CV values. After medical treatment for a mean follow-up period of 3.5 months, LV functions were evaluated again. Patients in the low CV group showed significant increase in LVEF from 30.7% to 50.6%, while LVEF of patients in the high CV group remained similar (37.6% to 35.8%, ns). An inverse correlation was observed between delta LVEF and CV, while no correlation was observed between delta LVEF and mean-rMGU. The results suggest that the wall motion reversibility of patients with IDC is associated with the spatial heterogeneity of rMGU, but not with initial absolute rMGU.

Key words: positron emission tomography, ^{18}Fluorine-Fluorodeoxyglucose, idiopathic dilated cardiomyopathy

略語一覧：FDG-PET：positron emission tomography with ^{18}Fluorine-Fluorodeoxyglucose
IDC：idiopathic dilated cardiomyopathy
rMGU：regional myocardial glucose utilization rates
CV：coefficient of variance

I. Introduction

Prediction of the effectiveness of medical treatment on left ventricular function is clinically important, but is very difficult in patients with idiopathic dilated cardiomyopathy (IDC). In ischemic heart disease, positron emission tomography (PET) has been validated as a reliable modality for assessing myocardial viability by the evaluation of left ventricular (LV) wall motion reversibility [1-8]. Although several reports have docu-

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mented the diagnostic utility of PET in IDC [9-12], only one report described its utility in predicting LV wall motion reversibility[13]. Generally, patients who show progressive LV dysfunction in spite of medical treatment are potential candidates for cardiac transplantation. Thus, it would be very helpful if LV wall motion reversibility can be predicted before starting medical treatment. The aim of this study was to investigate whether the improvement of left ventricular function could be predicted in IDC patients with severe LV dysfunction by quantitative FDG-PET study.

Ⅱ. Patients and Methods

Study population

This retrospective cohort study comprised twenty patients (15 men and 5 women, age range 19-72 years) with IDC treated medically for left ventricular dysfunction (Table 1). None of them showed abnormal findings in coronary angiograms. Patients with diabetes mellitus were excluded. The study protocol was approved by the PET safety committee of Chiba University School of Medicine. Written informed consent was obtained from each patient. All patients were medicated with inotropic agents including digitalis, and/or diuretics, and/or angiotensin-converting enzyme inhibitors. Inotropic agents, diuretics, angiotensin-converting enzyme inhibitors (ACEIs), and beta-blockers were given to 13 (65%), 16 (80%), 19 (95%) and 4 patients (20%), respectively (Table 2). The kinds of medication were not significantly different between the two groups.

Table 1 Patient Baseline Clinical Data

				before		after			mean-rMGU	
No.	age	sex	NYHA	LVDd (mm)	EF (%)	LVDd (mm)	EF (%)	medication	(μmol/min/g)	CV
1	45	M	I	71	45.5	71	39.6	A	0.8881	0.194
2	61	F	Ⅲ	46	29.2	48	57.8	Dig	0.9805	0.111
3	45	M	Ⅲ	74	22.4	71	33.4	A, D, Dig	0.7352	0.089
4	53	M	Ⅳ	80	48.8	60	60.6	A, D, Dig	0.5729	0.247
5	72	M	Ⅱ	57	40.3	75	39.3	A, D, Dig	0.3416	0.259
6	63	M	Ⅳ	64	43.2	61	38.1	A, D, Dig	0.554	0.142
7	31	M	Ⅳ	73	34.7	54	70.4	A, D, Dig	0.7376	0.089
8	36	M	I	63	17.9	59	52.6	A, Dig	0.5071	0.126
9	63	F	Ⅳ	67	24.5	70	30.5	A, D	0.707	0.12
10	63	F	Ⅳ	69	30.7	78	21.3	A, D	0.9184	0.214
11	19	M	Ⅳ	68	34.7	60	18.7	A, D, Dig, B	0.7403	0.159
12	56	M	I	55	45.2	58	29.8	A, D, Dig	0.6119	0.159
13	48	M	Ⅳ	61	38.1	57	70.4	A, D, Dig	0.5821	0.069
14	68	M	Ⅳ	80	24	70	43.1	A, D	0.2488	0.335
15	43	M	Ⅳ	60	45.5	55	61.5	A, D	0.3761	0.112
16	48	M	Ⅲ	79	30.7	75	55.6	A, D, Dig, B	0.8085	0.206
17	40	F	Ⅳ	65	29	65	36.1	A, D, Dig, B	0.605	0.128
18	57	M	Ⅱ	60	48.8	60	52.7	A	0.893	0.084
19	22	F	Ⅲ	50	36.4	54	31.5	A, D, Dig, B	0.3298	0.173
20	60	M	I	69	16.4	71	39.6	A, D	0.806	0.0067

A, Angiotensin converting enzyme inhibitors; Dig, Digitalis; D, Diuretics; B, beta blockers

Tnble 2 Medical treatment

	ACEIs	Digitalis	Diuretics	Beta blockers
High CV (n=10)	10	7	9	3
Low CV (n=10)	9	6	7	1
High rMGU (n=10)	9	5	7	2
Low rMGU (n=10)	10	8	9	2
n=20	19	13	16	4

ACEIs, Angiotensin converting enzyme inhibitors

Study protocol

Baseline transcutaneous 2-dimensional echocardiograghy was performed when the patients were hospitalized, and the follow-up study was performed under compensated condition after medical treatment. The interval between the 2 echocardiographies ranged from 1 to 59 months, with a mean of 3.5 months. The period did not differ significantly between the two groups. PET imaging was also performed within 1 week after the baseline echocardiography.

Echocardiography

LV wall motion was evaluated by LV long-axis and short-axis view. The internal diameter in diastole (LVDd) and systole (LVDs) of the left ventricule and intraventricular septal and left ventricular posterior wall thickness were also measured by M-mode tracing. The LV ejection fraction (LVEF) was calculated by Pombo's method and percent fractional shortening (%FS) was calculated by the following equation. %FS = (LVDd-LVDs)/LVDd × 100. Delta LVEF was also defined by the following equation: Delta LVEF=LVEF before the medical treatment−LVEF after the medical treatment.

Positron emission tomography

PET images were obtained with a SET-130W PET scanner (Shimadzu Co., Kyoto, Japan). This scanner can obtain three slices simultaneously with a slice thickness of 16.5mm, and the spatial resolution is 10.5mm-at full width at half maximum (FWHM). Effective in-plane resolution is 12.8mm FWHM after a smoothing filter is used. To ensure adequate myocardial uptake of the tracer, 75g of glucose was orally given 60 min before the administration of FDG. Then, plasma glucose, plasma immunoreactive insulin (IRI) and non-esterified fatty acid (NEFA) were measured at the time of FDG administration. Transmission data were acquired to correct for photon attenuation before obtaining PET emission data. Dynamic PET acquisition of the heart was started with the intraveneous administration of FDG (140 Mbq), and images were obtained for 63 min at 3 frames of 1 min duration followed by 5 frames of 2 min duration, 11 frames of 4 min duration and 1 frame of 6 min duration. Each PET image was corrected for dead time and physical decay of FDG.

Determination of rMGU

To determine myocardial time activity curves, 30 to 42 regions of interest (ROIs) with an area of 0.36cm^2 each were drawn on the left ventricular myocardium at the mid-ventricular level. ROIs were drawn on the last images of uptake and then projected to the early dynamic images. The ROIs were divided into six segments (posteroseptum, anteroseptum, anterior, anterolateral, midlateral, posterolateral regions). Arterial input function was obtained from the ROI in the center of the left atrial cavity. Patlak graphic analysis was performed to calculate regional myocardial glucose utilization rates (rMGU) using the serial ^{18}F activity in myocardial and

blood-pool ROIs[14,15]. The mean K value for each segment was used for further calculations. The rMGU in each segment is given by rMGU=K×Pglc/LC, where Pglc is the plasma concentration of glucose and LC (=0.67) is a correction factor for differences in the transport and metabolism of FDG and glucose[16-21]. To correct the recovery coefficient of the myocardium and the spillover from the blood pool to the myocardium, we used the constant fractions of 0.63 and 0.18, respectively, assuming that the left ventricular wall thickness was 10mm. The mean value and standard deviation of absolute rMGU were determined for each subject. The coefficient of variance (CV) of rMGU was calculated to assess the spatial heterogeneity of rMGU. We determined the ratio of the standard deviation to the mean value of six myocardial segments for rMGU in each subject.

Statistical analysis

Two-tailed paired Student *t* test was used for comparisons between the groups. Spearman correlation coefficients were used to evaluate the relation between delta LVEF and mean-rMGU and that between delta LVEF and CV. A probability value less than 0.05 was considered statistically significant.

Ⅲ. Results

Metabolic conditions

Plasma glucose, IRI and NEFA levels were within normal limits in all patients. These values were similar between the low CV group and the high CV group (Table 3).

PET measurements

The mean rMGUs in 20 patients ranged from 0.25 to 0.98 μmol/min/g, and the median was 0.653 μmol/min/g. We then divided the patients into two groups, one with patients with a mean rMGU greater than the median value (high rMGU) and the other with a mean rMGU below the median value (low rMGU) by PET examination. The median CV of rMGU before randomization was 0.135 in the 20 patients. Then, we also divided the patients into two groups of those with CV greater than the median value (high CV) and those with CV below the median value (low CV) by PET. Mean rMGU of the low CV group was 0.71±0.18 μmol/min/g and that of the high CV group was 0.60±0.24 μmol/min/g, and the difference was not significant.

Table 3 Metabolic and hormonal levels

	high CV	low CV	p value
FBS (mg/dl)	110.7±27.5	98.4±11.2	ns
BS 60°	164.2±25.7	161.8±27.8	ns
BS 90°	159.2±33.8	139.9±31.2	ns
BS 120°	153.8±40.3	126.3±29.8	ns
IRI 60° (μg/ml)	61.0±36.2	63.8±38.6	ns
IRI 90°	55.7±34.9	56.8±27.9	ns
IRI 120°	51.2±30.5	47.2±29.2	ns
NEFA 60° (mmol/l)	0.17±0.08	0.16±0.11	ns
NEFA 90°	0.13±0.05	0.10±0.04	ns
NEFA 120°	0.10±0.05	0.10±0.06	ns

FBS, fasting blood sugar; BS, blood sugar; IRI, plasma immunoreactive insulin; NEFA, plasma non-esterified fatty acid

Echocardiographic measurements

At baseline echocardiography, LVDd, LVEF and LVFS did not differ statistically between the two groups divided by CV value. No significant differences were observed in LVDd and LVEF between the low and high CV groups both in the baseline and the follow-up echocardiography studies (Fig 1a). LVEF in the low CV group improved significantly ($p=0.0051$), whereas that of the high CV group remained about the same (Fig 1b).

LVEFs of the patients in the high and low rMGU groups before medication were 31.9±10.1% and 36.4±10.8%, and LVDds of patients in the high and low rMGU groups were 67.6±9.1mm and 63.5±9.8mm, respectively (Fig 2a, b).

As shown in Fig 3, an inverse correlation was observed between improvements in LV wall motion (delta LVEF) and CV. While none of the patients in the low CV group deteriorated, seven patients in the high CV group declined. As shown in Fig 4, no correlation was observed between delta LVEF and

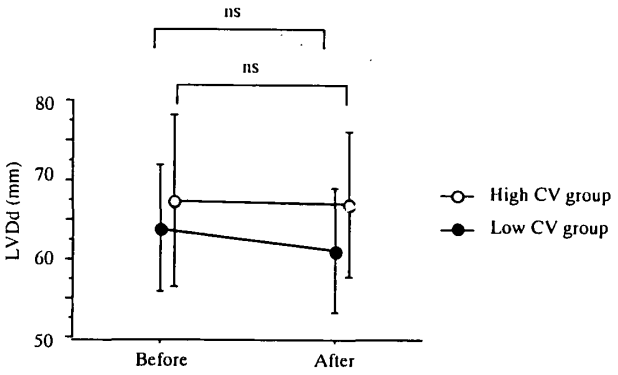

Fig 1a
Changes in LVDd in each group of patients with IDC (High CV group and Low CV group).

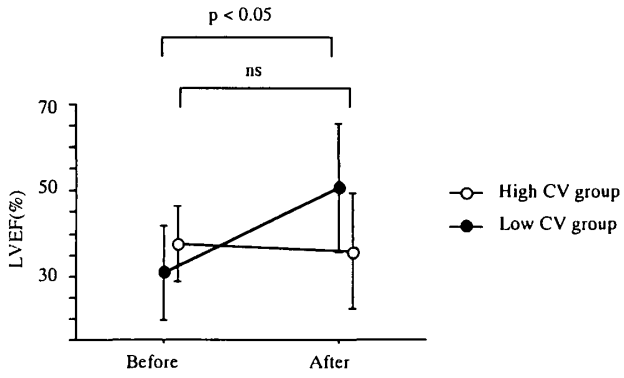

Fig 1b
Changes in LVEF in each group of patients with IDC (High CV group and Low CV group).

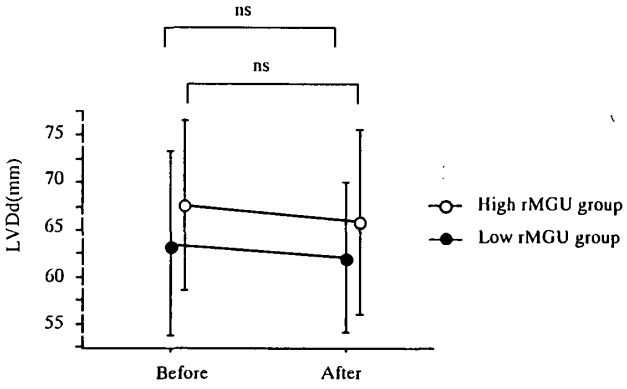

Fig 2a
Changes in LVDd in each group of patients with IDC (High rMGU group and Low rMGU group).

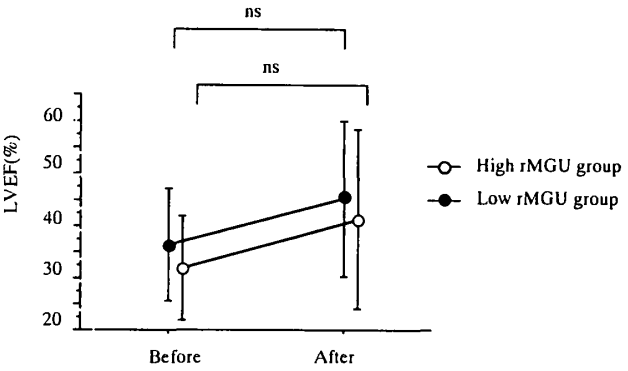

Fig 2b
Changes in LVEF in each group of patients with IDC (High rMGU group and Low rMGU group).

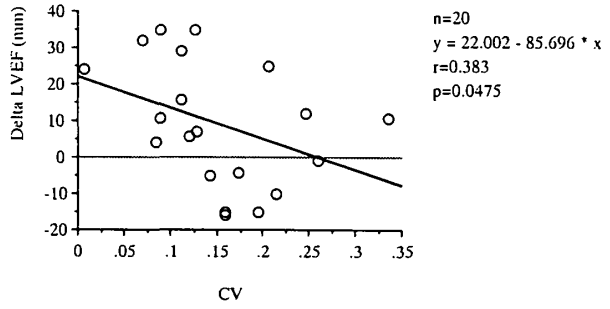

Fig 3
An inverse correlation was observed between improvement in left ventricular wall motion and coefficiency of variation of regional myocardial glucose utilization.

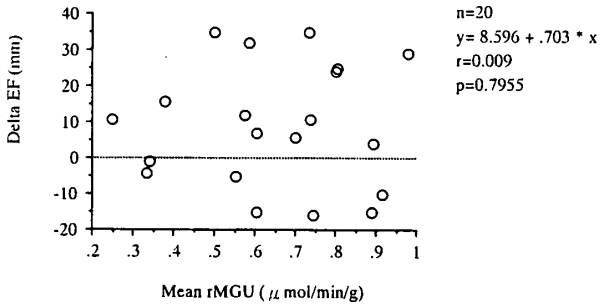

Fig 4
No correlation existed between delta left ventricular ejection fraction and mean regional myocardial glucose utilization.

mean-rMGU. Delta LVEF ranged from −16.0% to +35.7%.

Correlation between LVEF and LVDd

LVDd in all patients at the first study ranged from 46mm to 80mm. These was no correlation between delta LVEF and LVDd in the decompensated phase. LVEFs did not improve even when LVDds were small at the first study.

IV. Discussion

The major finding of the present study was that the coefficient of variance of rMGU predicted the LV wall motion reversibility in medically treated IDC patients. We also found that there was no association between LV wall motion reversibility and mean rMGU in these patients. These results suggest that LV wall motion reversibility in medically treated IDC patients was associated with the spatial heterogeneity of myocardial glucose utilization, not with the mean rMGU.

Previous studies suggested that IDC patients showed relative homogeneity in glucose and palmitate metabolism compared to ischemic heart disease especially in patients with myocardial infarction[10,22-24]. On the other hand, a few reports showed heterogeneity in glucose metabolism in patients with IDC[9, 11,13]. Our observation showed that the heterogeneity of myocardial glucose utilization ranged widely in IDC patients, and patients whose coefficient of variance of rMGU was below the median showed significant increase of LVEF after medical treatment. On the other hand, patients whose coefficient of variance of rMGU was above the median showed little change post medical treatment. We recently reported that the prognosis of IDC patients was associated with the spatial heterogeneity of myocardial perfusion, not with the mean myocardial blood flow[25]. Although the prognosis and LV wall motion reversibility after the medical treatment are different clinical issues, the progression of this disease would underlie the poor prognosis and poor response to medical treatment. Thus, our data suggest that the heterogeneity of myocardial glucose utilization and perfusion may reflect the progression of this disease.

In our previous study, mean myocardial blood flow at rest did not differ significantly between non-survivors and survivors. Moreover, myocardial blood flow at rest showed a tendency to be higher in non-survivors. It is speculated that increased activity of the sympathetic nervous system and myocardial oxygen requirements may have normalized myocardial blood flow to compensate for the reduction in myocardial perfusion at a certain stage of IDC. This mechanism may also underlie the result that mean rMGU could not predict LV wall motion reversibility.

The relation between myocardial perfusion and glucose uptake as well as a regional shift to preferred fatty acid utilization, a regionally altered transmembranous glucose transport or phosphorylation by hexokinase might be other mechanisms that would explain the heterogeneity of glucose utilization. Further studies will be needed using other metabolic tracers, such as ^{11}C palmitate, ^{11}C hydroxyephedrine

and ^{11}C acetate[9]. Although the mechanisms of the heterogeneity of myocardial glucose utilization and its relation to medical treatment are still unclear, the results demonstrated that LV wall motion reversibility after medical treatment could be predicted by FDG-PET. This method may provide additional information for patient selection of cardiac transplantation performed for IDC patients for whom medical treatment is not effective.

V. Conclusion

We conclude that the wall motion reversibility of patients with IDC is associated with the spatial heterogeneity of rMGU, not with initial absolute rMGU.

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要　旨

虚血性心疾患に関しては，現在までに FDG-PET を用いた左室壁運動改善の可能性の予測について報告されてきた。しかしながら拡張型心筋症の左室機能の改善と心筋糖代謝との関係は議論されていない。心臓超音波検査にて左室駆出率の低下している拡張型心筋症20症例（平均左室駆出率34.1±10.4%）に経口による糖負荷 FDG-PET を施行した。さらにそれぞれの症例で心筋糖代謝率とその不均一性の指標として変動係数（CV）を算出した。その中央値0.128をこえる変動係数を示す群（高 CV 群：10例）とそれ以下の群（低 CV 群：10例）の2群に分割し，薬物治療後に再び心臓超音波検査を施行してそれぞれの群における心機能の変化を検討した（平均3.5ヶ月後）。低 CV 群は平均左室駆出率が平均で30.7%から50.6%と有意に改善を認めた一方，高 CV 群は平均で37.6%から35.8%と改善を認めなかった。また左室駆出率の変化と平均心筋糖代謝率の間には相関が認められないものの，左室駆出率の変化と CV との間には負の相関を認めた。これにより拡張型心筋症症例における左室壁運動の改善は平均の心筋糖代謝率ではなく心筋糖代謝率の不均一性と関係している可能性が示された。この FDG-PET を用いた左室機能改善の予測は，治療方針の選択に役立つと考えられた。

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